61. (New) The method according to Claim 60 wherein the cancer is breast cancer.

REMARKS

Rejection of Claims 1, 3, 4, 15, 16, 19-23, 31 and 32 under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 15, 16, 19-23, 31 and 32 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the office action of 5-24-99" (Office Action, page 3).

The Examiner states that "Claims 1, 33, 44 and 49 and claims dependent therefrom are rejected for reasons of record because applicants have not enabled performing the method *in vivo* or other *in vivo* embodiments" (Office Action, page 3). The Examiner further states that "Claims 13, 39, 45 and 50 are directed toward producer cells but are not limited to isolated producer cells" and the Examiner suggests amending the claims to recite "isolated producer cells" (Office Action, page 3).

The claims have been amended to recite "isolated producer cells" as suggested by the Examiner.

It is the Examiner's opinion that the "specification does not provide adequate guidance correlating the results obtained *in vitro* to results obtained *in vivo* in such a way that one of skill would have a reasonable expectation in obtaining a therapeutic level of expression of SDI-1 such that cancer or restenosis could be treated" (Office Action, page 3). The Examiner states that the "specification does not teach the level of SDI-1 required to obtain a therapeutic effect, the dosage, route of administration or the desired therapeutic effect such that one of skill would be able to determine how to use the retroviral vector as a pharmaceutical composition" and that "it is unclear what therapeutic effect can be obtained by obtaining more cells in G_0/G_1 or how bladder carcinoma correlates to breast cancer (claim 23) or restenosis (claims 22 and 28)" (Office Action, pages 3-4). The Examiner states that the "dosage, mode of administration and vehicle of delivery are parameters which are essential to the invention and would require undue experimentation to determine given the unpredictability in the art" (Office Action, page 4). In addition, the Examiner states that the "only disclosed use for encapsulated cells and pharmaceutical compositions in the specification is for administering the cells *in vivo* to obtain

therapeutic effects" and that the "administration of replication competent retroviral packaging cells would most likely result in toxic, non-therapeutic results" (Office Action, page 5). Finally, the Examiner states that the "specification does not teach the dosage, route of administration, level of retroviral particles secreted or level of SDI-1 expression required *in vivo* to use encapsulated retroviral packaging cells tot treat any disease" (Office Action, pages 5-6).

Applicants respectfully disagree. As pointed out in the previously field amendments, the art of record establishes that based on Applicants' data, one of skill in the art would reasonably expect that producer cells stably transfected with a retroviral particle comprising a DNA sequence encoding SDI-1, retroviral particles produced by such a cell line and capsules which encapsulate such producer cell lines can be used to treat diseases or disorders responsive to the anti-proliferative activity of SDI-1 (cancer, restenosis). However, the Examiner has not responded directly to Applicants' statements to this effect made in the previously filed Amendment. Furthermore, the Examiner has not provided evidence to show that undue experimentation is required to determine dosage and mode of administration for a method of treatment.

Applicants' *in vitro* data demonstrating that a human bladder carcinoma derived cell line transfected with a gene encoding SDI-1 showed significantly more cells in G_0/G_1 (specification, page 26, lines 20-22) enable a person of skill in the art to use the claimed invention *in vivo*. As Applicants teach in the specification as filed and as known by those of skill in the art, a protein which affects cell cycle progression by causing the cell to be in a G_0/G_1 stage, can be used to inhibit proliferation of cells, particularly malignant cells. For example, Nabel *et al.* teach that expression of p21 which is "also known as WAF1, CIP1 or SDI" (Nabel *et al.*, column 1, lines 22-23), that "resulted in an accumulation of cell in G_0/G_1" and that "the growth of malignant cells in vivo is inhibited by expression of p21" (Nabel *et al.*, abstract). In addition, Harper *et al.* teach that inhibitors such as CIP1 represent a general strategy employed to control cell proliferation in response to external signals and developmental programs (Harper, *et al.*, *Cell*, 75:805-816 (1993) (Reference AZ of PTO 1449)).

Nabel *et al.* showed that expression of p21 inhibited vascular cell proliferation and induced cell cycle arrest *in vitro* (Nabel *et al.*, column 7, line 59 - column 8, line 60) and that these *in vitro* results correlated to their *in vivo* results using restenosis (Nabel *et al.*, Example 1)

and tumorigenicity animal models (Nabel *et al.*, Example 2; see also Nabel *et al.*, column 8, line 61 - column 11, line 7). Nabel *et al.* teach that p21 "inhibits the proliferation of intimal smooth muscle cells and significantly limits the development of neointima" and that "p21 expression completely suppressed the growth of tumors in all animals inoculated" (Nabel *et al.*, column 10, lines 53-55).

Furthermore, as noted by the Examiner, Miller *et al.* teach that "retroviruses can be used in vivo" and Price *et al.* demonstrate that "retroviral particles can be used to deliver gene of interest *in vivo*" (Office Action, page 9). Indeed, Miller *et al.* clearly teach that retroviral vectors "will be useful for the treatment of humans" (Miller *et al.*, page 989, column 3).

Finally, Applicants maintain that their teaching in the specification as filed that "dosage depends upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician in charge" (specification, page 19, lines 8-12), enables one of skill in the art to practice the claimed invention. Those of skill in the art, such as physicians, routinely determine the appropriate dosage for a particular treatment protocol. For example, one likely mode of administration is injection of the claimed retroviral particles or capsules. The Examiner has provided no evidence to establish that undue experimentation is required for a person of skill in the art to determine dosage and mode of administration for a method of treatment.

Applicants maintain that the Examiner has failed to provide evidence to show that one skilled in the art would not accept Applicants' *in vitro* data as reasonably correlating to the use of the claimed methods *in vivo*, or that one of skill in the art would require more than routine methods to determine dosage and mode of administration. Applicants have provided an enabling disclosure for performing the claimed methods *in vivo*.

The Examiner states that "Applicants have enabled one of skill to determine amino acids 1-71 or 42-58 of the human SDI-1 gene disclosed in WO 95/06415 but not any other human SDI-1, WAF-1, CIP1, PCI1 or p21 sequence disclosed in the art" (Office Action, page 4). The Examiner further states that "[i]t is not clear that any other amino acids of human SDI-1, WAF1, CIP1, PIC1 or p21 would have the same amino acid sequence or function as amino acids 1-71 or 42-58 described in WO 95 06415" and that the "amino acid sequence encoding SDI-1, WAF1, CIP1, PIC1 or p21 varies in the art" (Office Action, pages 4-5).

Applicants respectfully disagree. As Applicants state in the specification as filed, "[o]ther groups have described SDI-1 as WAF1, CIP1; PIC1 and p21" and cite references in support thereof (specification, page 2, line 2). As such, Applicants have enabled those of skill in the art to use amino acids 1-71 or 42-58 of these other proteins because human SDI-1 has the same amino acid sequence as these other descriptions of the human SDI-1 protein. For example, Applicants direct the Examiner's attention to the human WAF-1 amino acid sequence in Figure 3 of El-Deiry *et al., Cell, 75:*817-825 (1993) (Reference AR2 of PTO 1449), the human Cip1 amino acid sequence in Figure 2 of Harper, *et al., Cell, 75:*805-816 (1993) (Reference AZ of PTO 1449), and the human p21 amino acid sequence in Figure 1 of Xiong, *et al., Nature, 366:*701-704 (1993) (Reference AS2 of PTO 1449), which all show the same amino acid sequence as the amino acid sequence of SDI-1. In addition, the Hunter (*Cell, 75:*839-841 (1993), Reference AT2 of PTO 1449) notes that the "Sequence of Waf1 is identical to Cip1" and that the "size and peptide map of Pic1 are the same as those of the 21 kd protein (p21) that is found associated with most cyclin-Cdk complexes in normal cells. . . . suggesting that the two proteins are the same" (Hunter, page 840, column 1).

The Examiner further states that the "specification has not taught any method to identify functionally useful analogues or fragments of the human SDI-1 gene taught in WO 95/06415" (Office Action, page 5).

Applicants respectfully disagree. As the Examiner notes, Applicants have enabled functional fragments of human SDI-1, *e.g.*, amino acids 1-71 and amino acids 42-58 of the human SDI-1 protein (see, for example, page 8, line 22 - page 9, line 4). Additional fragments and methods for determining the capacity of such fragments to inhibit DNA synthesis are also clearly described in the specification (*e.g.*, see page 9, lines 5-12 and the exemplification of the specification). Furthermore, Applicants provide guidance to a person of skill in the art to identify analogues of SDI-1 (specification, page 9, lines 13-24). Applicants maintain that it is well within the skill in the art to identify analogues of a protein of known sequence using the guidance provided by Applicants in the specification as filed. In addition, using routine methods one of skill in the art can identify potential analogues which hybridize (*e.g.*, under moderate or high stringency) to the known sequence of SDI-1. Hybridizing sequences can then be introduced into cells (*e.g.*, see Example 4 of the specification), and the stage of the cells can be determined

wherein cells in G_0/G_1 indicate that the cells in which DNA synthesis is inhibited (*e.g.*, see page 9, lines 5-12 and/or Example 5 of the specification).

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 31 and 32 under 35 U.S.C. §112, second paragraph

Claims 31 and 32 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 6). The Examiner states that the "claims recite limitations wherein the recombinant retroviral particle is administered as an injection or by implantation of a packaging cell line", however, "the claims refer to claim 28 which is limited to delivery of a packaging cell lines" (Office Action, page 6). The Examiner states it is "unclear whether applicants intend to claim administering retroviral particles or retroviral packaging cells" (Office Action, page 6).

Claims 31 and 32 have been amended to more clearly indicate that a recombinant retroviral particle is administered as an injection, or that a recombinant retroviral particle is administered by implantation of a packaging cell line.

Rejection of Claims 1-4, 9, 13, 19, 26, 33, 34, 39, 43, 44, 45, 48, 49, 50 and 53 under 35 U.S.C. §102(b)

Claims 1-4, 9, 13, 19, 26, 33, 34, 39, 43, 44, 45, 48, 49, 50 and 53 are rejected under 35 U.S.C. §102(b) as being anticipated by the Tsang *et al.* reference. The Examiner has considered Applicants' statements in the previously filed Amendment, however, the Examiner states that the "p21 protein of Tsang is the same as the SDI-1 protein disclosed in the instant invention and encodes SDI-1 protein, which inherently comprises amino acids 1-71 and 42-58 as claimed and inherently inhibits cell proliferation" (Office Action, page 7).

Applicants respectfully disagree. The ras p21 protein of Tsang *et al.* is ***not*** the same as the SDI-1 protein of the subject application. The ras p21 protein and the SDI-1 protein differ in their function, amino acid sequence and chromosomal localization which is illustrated below in a comparison of the ras p21 and SDI-1 house mouse sequences.

The gene *Hras* encodes the transforming protein p21/H-RAS-1, which is a *protooncogene* capable of binding GTP (see, for example, the Pincus *et al.* Abstract being filed herewith as Exhibit A). Hras1 is localized on mouse chromosome 7 and has the nucleotide sequence shown in NCBI Accession No. NM_008284, entitled "Mus musculus Harvey rat sarcoma virus oncogene (Hras1), mRNA" (submitted herewith as Exhibit B), and the amino acid sequence shown in NCBI Accession No. Q61411, entitled "Transforming protein p21/H-Ras-1 (C-H-Ras)" (submitted herewith as Exhibit C).

In contrast, the SDI-1 gene encodes a cyclin-dependent kinase inhibitor which has also been designated p21. As pointed out above, the p21 cyclin-dependent kinase inhibitor is also known as SDI-1, WAF1 and CIP1. p21 (a.k.a. SDI-1) is localized on chromosome 17 and has nucleotide and amino acid sequences which differ from the sequences of ras p21 as shown in Accession No. U09507, entitled "Mus musculus p21 (Waf1) mRNA, complete cds" (being filed herewith as Exhibit D). This p21 protein (a.k.a. the SDI-1 protein) is important for regulation of the cell cycle, particularly of the interphase, *i.e.*, the period between the division of the cell into two daughter cells, which is called mitosis. The interphase is divided into different phases, gap1 (G1), synthesis of DNA (S) and gap2 (G2). The SDI-1 encoded protein p21 induces G1 arrest and blocks entry into S phase, *i.e.*, the DNA synthesis is blocked. Consequently, SDI-1 is an antitumor gene (see, for example, description, page 2, 1st paragraph and enclosed abstract by Gartel *et al.*).

Applicants have clearly established that the p21 protein of Tsang *et al.* is not the same protein as the SDI-1 based on the differences in their function, amino acid sequence and chromosomal localization. Tsang *et al.* do not teach Applicants' claimed "polypeptide with SDI-1 activity of inhibiting cell proliferation".

Tsang *et al.* do not anticipate Applicants' claimed invention.

Rejection of Claims 1-4, 8, 13, 14, 19, 26-28, 31 and 32 under 35 U.S.C. §103(a)

Claims 1-4, 8, 13, 14, 19, 26-28, 31 and 32 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Miller *et al.* or Price *et al.* in view of Nable *et al.* In response to Applicants' position, the Examiner states that "Miller and Price teach stably transfecting producer cell lines" and that stably transfected does not differ from the transiently transfected producer cells of Nabel because they are stably transfected for a short amount of time" (Office

Action, page 9). It is the Examiner's opinion that "'Stably transfected' does not exclude temporarily, stably transfected cells as taught by Nabel" (Office Action, page 9).

Applicants respectfully disagree. Transfection is defined as the introduction of a foreign, essentially protein-free nucleic acid sequence into cells, and is characterized as stable *or* transient transfection. Stable transfection indicates that ***the sequence of interest is integrated into the genome of the transfected cell*** (see, for example, Watson *et al.*, "Recombinant DNA", Witkowski and Zolev, 2nd ed., pages 216-218 (1992), which is being field herewith as Exhibit E). Stably transfected cells transmit the integrated sequence of interest to daughter cells.

In contrast, transient transfection indicates that the sequence of interest is taken up by the transfected cell, however, ***the sequence is not integrated into the genome of the transfected cell*** (see Exhibit E). As a result, with transient transfection the sequence of interest persists in the producer cell for only a short period of time and disappears after some days. Transiently transfected producer cells do not transmit the new DNA to daughter cells. Therefore, stably transfected cells exclude temporarily, *i.e.*, transiently transfected cells.

For long term expression of a sequence stable transfection is required. Furthermore, transfection is a very inefficient process and the transfection efficiency is directly correlated with the number of retroviral particles produced by a cell culture system (see, for example, WO 00/66758). Stable transfection has the advantage that after the initial transfection the transfected cells only need to be amplified and no further transfection is required. However, stable expression of the sequence of interest is only possible when the protein encoded by the sequence of interest does not inhibit basic functions of cell (*e.g.*, DNA synthesis). Otherwise, a stable cell population for production of the protein cannot be obtained.

Where the claimed invention is rejected as obvious in view of a combination of references, 35 USC § 103 requires not only that the prior art would have suggested to the person of skill in the art that they should carry out the claimed process, but "that the prior art should establish a reasonable expectation of success" (*In re Vaeck* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). There must also be motivation or suggestion in the prior art to combine elements in the prior art. That is, in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art (*In re Newell* 13 USPQ2d 1248, 1250 (Fed. Cir. 1989)).

As pointed out in the previously filed Amendment, the combined teachings of Miller *et al.*, Price *et al.* and Nabel *et al.* do not teach or suggest *stably* transfecting packaging cells (*i.e.*,

293 cells) with a retroviral vector comprising DNA encoding SDI-1 which additionally harbors at least one DNA construct coding for proteins required for said retroviral vector to be packaged, wherein RNA molecules are packaged into viral particles and released by *budding* from the packaging cells.

At the time of Applicants' invention, it was well known in the art that SDI-1 inhibits DNA synthesis, *i.e.*, one of the essential processes in a cell. Therefore, it would not be obvious to produce a recombinant retroviral particle by stably transfecting a cell with a sequence with SDI-1 function to the person of skill in the art, since the person of skill would expect the cell to be severely damaged as soon as the protein is produced (and would thus be unable to produce retroviral particles) due to inhibition of DNA synthesis. Clearly a person of skill in the art would not be motivated to attempt stable transfection a cell with the SDI-1 sequence to produce retroviral particles.

However, Applicants show that a vector encoding SDI-1 function can be stably transfected into a producer cell and that, surprisingly, a stable producer cell population can be established. In this case, recombinant viruses are produced although SDI-1 protein is expressed. Thus, in contrast to the teachings of the cited art Applicants' claimed invention provides an efficient method for producing retroviral particles encoding SDI-1 function. According to Applicants' claimed invention, once stably transfected producer cells are obtained retroviral particles are produced simply by maintaining and amplifying the producer cell population and the inefficient transfection process is avoided.

Clearly, the teachings of Miller *et al.*, Price *et al.* and Nabel *et al.*, either alone or in combination, do not teach or even suggest a method for producing a recombinant retroviral particle, said particle comprising a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof wherein the SDI-1 or functional fragment or functional analogue thereof inhibits cell proliferation, comprising *stably transfecting* a producer cell with *a retroviral vector* comprising the DNA sequence, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged.

The teachings of Miller *et al.*, Price *et al.* and Nabel *et al.* do not render obvious Applicants' claimed invention.

Rejection of Claims 1, 9-11 and 36-38 under 35 U.S.C. §103(a)

Claims 1, 9-11 and 36-38 are rejected under 35 U.S.C. §103(a) as being unpatentable over Miller *et al.* or Price *et al.* in view of Nabel *et al.* as applied to claims above and further in view of Haertig *et al.* for reasons of record. In response to Applicants' statements regarding the lack of suggestion to combine the references made in the previously filed Amendment, the Examiner states that "the motivation to combine the references is to obtain mammary specific gene expression in treating breast cancer" (Office Action, page 11).

Applicants respectfully disagree. As discussed above, the teachings of Miller *et al.*, Price *et al.* and Nabel *et al.*, either alone or in combination, do not teach a method for producing a recombinant retroviral particle, said particle comprising a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof wherein the SDI-1 or functional fragment or functional analogue thereof inhibits cell proliferation, comprising *stably transfecting* a producer cell with *a retroviral vector* comprising the DNA sequence, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged. Nor do the teachings of Miller *et al.*, Price *et al.* and Nabel *et al.*, either alone or in combination, provide the motivation to do so.

At the time of Applicants' invention, it was well known in the art that SDI-1 inhibits DNA synthesis, *i.e.*, one of the essential processes in a cell. Therefore, it would not be obvious to produce a recombinant retroviral particle by stably transfecting a cell with a sequence with SDI-1 function to the person of skill in the art, since the person of skill would expect the cell to be severely damaged as soon as the protein is produced (and would thus be unable to produce retroviral particles) due to inhibition of DNA synthesis. Clearly a person of skill in the art would not be motivated to attempt stable transfection a cell with the SDI-1 sequence to produce retroviral particles.

Haertig *et al.* do not provide what is lacking in the combined teachings of the Miller *et al.*, Price *et al.* and Nabel *et al.* references. Haertig *et al.* "show that MMTV expression is regulated by cell density in GR mouse mammary cells but not in NIH 3T3 mouse fibroblasts"...and that this "effect is mediated by binding sites in the HRE for the transcription factors OTFI and CTF/NFI" (Haertig *et al.*, page 814, column 1). Haertig *et al.* do not provide any motivation to produce a recombinant retroviral particle, said particle comprising a DNA

sequence encoding SDI-1, a functional analogue, or a fragment thereof wherein the SDI-1 or functional fragment or functional analogue thereof inhibits cell proliferation, comprising *stably transfecting* a producer cell with *a retroviral vector* comprising the DNA sequence, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged. Furthermore, there is nothing in the Haertig *et al.* reference that would lead one of skill to expect that a *stably transfected producer cell line comprising a retroviral genome which encodes the SDI-1* could be produced

The teachings of Miller *et al.*, Price *et al.*, Nabel *et al.* and Haertig *et al.* do not render obvious Applicants' claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A method for producing a recombinant retroviral particle, said particle comprising [a DNA] an RNA sequence [encoding] which encodes SDI-1, or a functional analogue[,] or a functional fragment [thereof wherein the] of the RNA sequence which encodes a polypeptide with SDI-1 activity of inhibiting [or functional fragment or functional analogue thereof inhibits] cell proliferation, comprising stably transfecting [a] an isolated producer cell with a retroviral vector comprising [the] a DNA sequence which encodes SDI-1 or a functional analogue or functional fragment which encodes a polypeptide with SDI-1 activity of inhibiting cell proliferation, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged.

8. (Twice amended) The method of Claim 1, wherein the retroviral vector comprises a 5' LTR region of the structure U3-R-U5; one or more sequences selected from coding and noncoding sequences; and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence containing a regulatory element or a promoter, followed by the U5 and R region, characterized in that at least one of the coding sequences is a DNA sequence encoding SDI-1, a functional analogue thereof, or a functional fragment thereof, said sequence being under transcriptional control of said regulatory element or promoter.

9. (Twice amended) The method of Claim 1 wherein the DNA sequence encoding SDI-1, a functional analogue, or a functional fragment thereof, is under transcriptional control of a target cell specific regulatory element or a target cell specific promoter or an X-ray inducible promoter.

13. (Three times amended) [A] An isolated producer cell stably transfected with a retroviral vector comprising a DNA sequence encoding SDI-1, a functional analogue thereof, or a functional fragment thereof, wherein the SDI-1 or functional fragment or functional analogue thereof inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged.

26. (Three times amended) A method for introducing DNA sequences encoding SDI-1, a functional analogue, or a functional fragment thereof, into human cells in vitro comprising infecting a target cell population with a retroviral particle produced by the producer cell line of Claim 13.

31. (Amended) A method according to Claim 28 wherein the recombinant retroviral particle is administered as an injection, or the recombinant retroviral particle is administered by implantation of a packaging cell line harbouring:

a) a retroviral vector carrying a DNA sequence encoding SDI-1, a functional analogue, a fragment thereof or an antisense SDI-1 DNA sequence; and

b) at least one DNA construct coding for the proteins required for said retroviral vector to be packaged

into the living animal body, including a human, nearby or at the site of the tumor.

32. (Amended) A method according to Claim 28 wherein the recombinant retroviral particle is administered as an injection, or the recombinant retroviral particle is administered by implantation of an encapsulated packaging cell line comprising encapsulated cells having a core containing packaging cells harbouring:

a) a retroviral vector carrying a DNA sequence encoding SDI-1, a functional analogue, a fragment thereof or an antisense SDI-1 DNA sequence; and

b) at least one DNA construct coding for the proteins required for said retroviral vector to be packaged

and a porous capsule wall surrounding said core, said porous capsule wall being permeable to the retroviral particles produced by the packaging cells, into the living animal body, including a human, nearby or at the site of the tumor.

33. (Amended) A method for producing a recombinant retroviral particle, said particle comprising [a DNA] an RNA sequence [encoding] which encodes SDI-1, wherein the SDI-1 inhibits cell proliferation, comprising stably transfecting [a] an isolated producer cell with a retroviral vector comprising [the] a DNA sequence which encodes SDI-1 wherein the SDI-1 inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged.

39. (Amended) [A] An isolated producer cell stably transfected with a retroviral vector comprising a DNA sequence encoding SDI-1 wherein the SDI-1 inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged.

44. (Amended) A method for producing a recombinant retroviral particle, said particle comprising [a DNA] an RNA sequence which codes for amino acids 1 to 71 of human SDI-1 and inhibits cell proliferation, comprising stably transfecting [a] an isolated producer cell with a retroviral vector comprising [the] a DNA sequence which encodes SDI-1 wherein the SDI-1 inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged.

45. (Amended) [A] An isolated producer cell stably transfected with a retroviral vector comprising a DNA sequence which codes for amino acids 1 to 71 of human SDI-1 and inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged.

49. (Amended) A method for producing a recombinant retroviral particle, said particle comprising [a DNA] an RNA sequence which codes for amino acids 42 to 58 of human SDI-1 and inhibits cell proliferation, comprising stably transfecting [a] an isolated producer cell with a retroviral vector comprising [the] a DNA sequence which encodes SDI-1 wherein the SDI-1 inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for proteins required for said retroviral vector to be packaged.

50. (Amended) [A] An isolated producer cell stably transfected with a retroviral vector comprising a DNA sequence which codes for amino acids 42 to 58 of human SDI-1 and inhibits cell proliferation, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged.